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A retrospective review of factors associated with response to phototherapy and PUVA for atopic eczema

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There is randomised study evidence that narrowband ultraviolet B (NB-UVB) is effective for eczema.[1] A small controlled study did not detect an efficacy difference between bath 8-MOP PUVA (psoralen drug with the main effects limited to the skin as the drug is 'activated' there by ultraviolet A [UVA] exposure) and NB-UVB.[2] Another small randomised study showed that 5-MOP oral PUVA worked better than medium-dose ultraviolet A1 (UVA1).[3] A systematic review concluded that NB-UVB and ultraviolet A1 were the most effective phototherapies for eczema and pointed out the limited comparative evidence regarding PUVA.[4]

To guide our clinical use of the phototherapies, we assessed retrospectively the response to phototherapy (NB-UVB, UVA1 and PUVA) of atopic eczema in Tayside. This was part of local audit so Ethics committee approval was not needed.

We examined our local data, collected through PhotoSys (the database of the National Managed Clinical Network for Phototherapyhttps://www.photonet.scot.nhs.uk/) on 1532 (88%) NB-UVB, 83 (4%) PUVA and 129 (6%) UVA1 whole-body courses given to 1303 patients, with courses completed between February 2002 and January 2016. These

courses were given in 4 units (Dundee, Perth, Stracathro and St Andrews): all used NB-UVB (broadband UVB stopped being used in Tayside before 1990) and PUVA (oral, predominantly 8-MOP, and bath 8-MOP [rarely used for eczema as face usually needs treated]) but UVA1 was only available in Dundee. All units are part of the same phototherapy service, with treatment protocols identical in all parts of the service.

We took "moderate improvement", "minimal residual activity" or "cleared" recorded in Photosys as representing a good outcome and any other outcome (including "did not attend") as not a good outcome. The main outcome measure we assessed was probability of a "good outcome" over number of treatments per course. We assessed many covariates (Table 1) that might influence treatment efficacy. We used the chi-square test to compare proportions of discrete covariates and propensity scores were implemented with respect to the age and sex (variables hypothesized to be associated with both selected predictors and outcome). It was verified that the proportions and propensity scores were statistically balanced across all covariates' groups in the original study cohort. For simple comparison of "survival curves" we used the logrank test. We used multivariate (adjusting for sex and age, as recorded factors that might influence efficacy) frailty models for associations between the selected covariates and the probability of good outcome over the number of treatments per course, taking into account the correlation between outcomes of repeated courses within individuals.[5] Furthermore, this frailty model allowed us to incorporate both time variant covariates such as levels of cumulative UVB, PUVA, and UVA1 treatments and time invariant covariates such as the levels of skin photoype and gender. All statistical analyses were performed using R software version 3.4 (https://www.r-project.org/).

Most patients, 679 (74%), had one course, 175 (17%) had two, 46 (5%) of subjects had three and only 37 (4%) patients had more than three. The main findings are shown in **Table 1**. A total of 763 (59%), 272 (20%), 138 (10%), and 130 (9.9%) courses were conducted at Dundee, Perth, St Andrews, and Stracathro centres respectively, with good outcome proportions of 63.3%, 74.3%, 63%, and 69.2%.

We found PUVA associated with a greater chance of a good outcome than the other phototherapies, despite it nearly-always being a second- or third-line phototherapy. One of the 4 phototherapy units in Tayside was associated with better outcomes. Possibly,

this was connected with it (Perth) being the second-longest established unit and the longest-established being Dundee, the only unit also offering UVA1, a treatment often reserved for particularly difficult to treat patients. A unit being longer-established will often mean that a lower proportion of courses are given according to protocols, with more individualisation of treatment regimens. It seems likely that more individualisation of courses might be beneficial. This is yet an untested hypothesis: we did not collect data on proportion of individualised *versus* by protocol courses given in each centre in this retrospective review.

Having a painful erythema recorded was associated with more good outcomes. However, when we analysed taking into account number of treatments this effect disappeared suggesting that here the chances of having an important erythema may simply have been a marker for having sufficient treatments to benefit. Similarly, older patients appeared to fare better until we took into account number of treatments. Perhaps older patients were less likely to stop attending early.

Lower compared with higher cumulative exposures to UVB, UVA1 and to PUVA (although possibly with PUVA a chance finding – see **Table 1**) were associated with better responses. This may be because of keeping trying the treatments in those for whom they do not work well or there could be a genuine tachyphylaxis effect with the treatments becoming less effective with repeated courses.

In this population all were of low (I to III) Fitzpatrick sun-reactive skin phototypes, those of skin phototype II were slightly more likely to respond than those of phototype I. Similarly, although this did not reach statistical significance (see **Table 1**) those of skin phototype III may have done better. In Tayside, starting doses are decided by minimal erythema doses (for UVB and UVA1) or minimal phototoxic dose (for PUVA) repeated for each course but different phototypes can be associated with differences in the development of tolerance – perhaps different regimens for those of different phototypes would help or we could consider other methods to adjust individual doses during treatment courses.[6]

This was a retrospective review in a single area. It has, however, led to some altered practice with the clinical author now using PUVA earlier for eczema, although still usually

after failure of NB-UVB. Testing various hypotheses generated by our findings should help improve the use of these treatments for eczema.

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Table 1. Summary of data on most important variables assessed for possible effects on treatment outcome when treating eczema with the phototherapies

	Overall	Distribution of courses according to the outcome			RR (95% CI) for multivariate frailty model (probability of 'good outcome' by cumulative number of treatments per course)
Outcome (overall)	1303 courses	Not good outcome 441 (34%)	Good outcome 862 (66%)	P value	
Sex				0.44b 0.40c	
Female	689 (53%)	234 (34%)	455 (66%)		1
Male	614 (47%)	207 (34%)	407 (66%)		0.91 [0.76, 1.10]
Mean age at time of course	34	33 years	35 years	0.02b 0.73c	
High age ≥ 31.09 yrs (median)	653 (0.50)	202(30.93)	451 (69.07)		1
Low age	620 (0.50)	239 (36.77)	411 (31.54)		0.94 [0.79, 1.13]
Erythema				0.004b 0.60c	
No	1261 (0.97)	435 (34.50)	826 (65.50)		1
Yes	42 (0.03)	6 (14.29)	36 (85.71)		0.92 [0.69, 1.22]
History-based sun-reactive skin photoype				0.993b 0.001c	
I	875 (0.67)	297 (33.94)	578 (66.33)		1
II	401 (0.30)	135 (33.36)	266 (66.44)		1.33 [1.09, 1.62]
III	27 (0.02)	9 (33.84)	18 (66.67)		1.47 [0.77, 2.80]
Treatment Centre				0.007b 0.001c	
Dundee	763 (.59)	280 (36.70)	483 (63.30)		1
Perth	272 (0.20)	70 (25.74)	202 (74.26)		2.03 [1.64, 2.51]
St Andrews	138 (0.10)	51 (36.96)	87 (63.04)		1.28 [0.95, 1.72]
Stracathro	130 (0.099)	40 (30.77)	90 (69.23)		1.11 [0.84, 1.47]
Treatment Type				0.005b 0001c	
PUVA	61(.04)	22 (36.07)	39 (63.93)		1

UVA1	86(0.06)	43 (50.00)	43 (50.00)		0.19 [0.11, 0.33]
UVB	1156(0.88)	376 (32.53)	780 (67.47)		0.29 [0.19, 0.43]
Cumulative UVB				0.001b 0.001c	
High ≥ 48m	654 (50.19)	172 (26.30)	482 (73.70)		1
Low	642 (49.27)	266 (41.43)	376 (58.57)		2.07[1.73, 2.47]
Cumulative PUVA				0.830a 0.095b	
High ≥ 28m	185 (14.20)	65 (35.14)	120 (64.86)		1
Low	418 (32.08)	137 (32.78)	281 (67.22)		1.64[0.88, 1.55]
Cumulative UVA1				0.001b 0.001c	
High ≥ 33m	99 (7.6)	35 (35.35)	64 (64.65)		1
Low	107 (8.2)	60 (56.07)	47 (43.93)		2.47[1.34, 4.54]

a: (directly comparing proportions)

b: (from a multivariate frailty model taking into account cumulative treatment numbers and adjusted by sex and age)